A Novel Neuroprosthesis to Restore Bladder Function after SCI

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Neural Control of Micturition

Normal Condition

Urine Storage
- Bladder: relax
- EUS: contract

Voiding
- Bladder: contract
- EUS: relax

After Spinal Cord Injury

Urine Storage
- Bladder: contract
  i.e. detrusor hyperreflexia (DH)
- EUS: contract

Voiding
- Bladder: contract
- EUS: contract
  i.e. detrusor sphincter dyssynergia (DSD)
Detrusor Hyperreflexia

1. Bladder hypertrophy
2. Low bladder storage capacity
3. Frequent incontinence
4. Transient high intravesical pressure
5. Risk of kidney damage
Detrusor Sphincter Dyssynergia

1. Large residual volume of urine
2. Daily urethral catheterization
3. Frequent bladder/urethra infection
4. High intravesical pressure
5. Vesicoureteral reflux and renal failure in the long-term
SCI Fact Sheet (from CDC)

1. 200K SCI currently in US
2. 12K – 20K new SCI per year
3. Medical cost $15K - $30K per year
4. Life medical cost $0.5 - $3 MM per SCI
5. Causes:

- 46% Motor Vehicle Accidents
- 22% Falls
- 16% Violence
- 12% Sports

Pie chart showing the causes of SCI injuries.
### Treatment for Micturition Dysfunction

#### Implantable devices

<table>
<thead>
<tr>
<th>Sacral Neuromodulation</th>
<th>Sacral Anterior Root Stimulation</th>
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<tbody>
<tr>
<td>InterStim® Stimulator</td>
<td>Brindley Stimulator</td>
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<tr>
<td>Medtronic Inc. USA</td>
<td>Finetech Medical Ltd. UK</td>
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- Minimal surgery to implant a tined lead at the S3 sacral foramen
- Only treat DH
- For both spinal cord injured and spinal cord intact patients

- Major spinal surgery to implant electrode on S2-4 anterior root
- Treat both DH and DSD
- Requires dorsal rhizotomy
- Eliminates reflex defecation and sexual functions

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**Can we treat both DH and DSD without rhizotomy?**
Pudendal-to-Bladder Reflexes in Chronic SCI cats
Pudendal Nerve Neuromodulation of Bladder Activity

Electrical Stimulation at 0.5 – 1000 Hz
1. Inhibitory at 3-7 Hz
2. Excitatory at 20 Hz
Frequency Dependence - Isovolumetric

Stimulation:
0.1 ms
0.5 V

Bladder Volume:
110 mL
Stimulation: 0.1 ms, 10 V.
Bladder Capacity: 80 mL
Bladder Volume: 50 mL
Frequency Dependence – Cystometrogram (CMG)

Stimulation: 0.1 ms, 1 V
Infusion: 5 mL/min
Stimulation: 0.1 ms, 0.7-2 V
Infusion: 5 mL/min
N = 3
Summary

- At 3-7 Hz pudendal nerve stimulation can inhibit bladder activity, increase bladder capacity, and treat DH.

- At 20 Hz pudendal nerve stimulation can excite bladder and induce large bladder contraction, but co-activation of the sphincter (DSD) will prevent voiding.
Blocking Pudendal Nerve by Biphasic High-Frequency (6-10 kHz) Electrical Current
Pudendal Block to Relax EUS

Blocking Stimulation

Tripolar Electrode

2 mm

8 mm

Cut centrally

Blocking Frequency
6-10 kHz

Stim. B (exciting)

Stim. A (blocking)

Infusion Rate
1-2 ml/min

KIDNEY

URETER

(DRAINED EXTERNALLY)

URETHRA

PROSTATE

EUS MUSCLE

PUDENDAL NERVE

PENIS

Recorder

100 seconds

60 cmH2O

Stim. A

7K Hz, 4 mA, 0.05 ms

Stim. B

40 Hz, 3 V, 0.2 ms
Pudendal Nerve Block or Muscle Fatigue?

A

Stim. A

8 kHz, 2 mA

60 cm H₂O

Stim. B

40 Hz, 0.8 V, 0.1 ms, 2 sec on, 6 sec off

40 sec

Stim. A

8 kHz, 2 mA

Stim. B

40 Hz, 0.8 V, 0.1 ms, 2 sec on, 6 sec off

B

Stim. B (exciting)

C

Stim. A (blocking)

Pudendal Nerve

Cut centrally

Stim. B (exciting)

EUS
Nerve Conduction after Repeated Pudendal Block

Stim. A: 8K Hz, 2 mA, 1 min ON

Stim. B: 40 Hz, 0.8 V, 0.1 ms, 2 sec ON, 6 sec OFF, total 43 min
Summary

High-frequency (6-10 kHz) biphasic electrical stimulation can block pudendal nerve conduction and reduce urethral resistance.

Question:
Can this high-frequency stimulation be used to treat DSD?
Voiding in Chronic SCI Cats
by Stimulating and Blocking Pudendal Nerves
Control Bladder and EUS by Pudendal Nerve Stimulation and Blockade after Spinal Cord Injury

Bladder

External Urethral Sphincter (EUS)

Lumbar Sacral Pelvic Plexus

Hypogastric

Pelvic

Pudendal

3-7 Hz

20 Hz

6-10 kHz

Storage

Voiding

Bladder Pressure

EUS EMG Stimulation

Spinal Cord Injury

Lumbar

Sacral

Hypogastric

Pelvic Plexus

Pelvic

Pudendal

External Urethral Sphincter (EUS)

Bladder

Spinal Cord Injury

Storage

Voiding

Bladder Pressure

EUS EMG Stimulation
Voiding Induce by Bladder Distension

A. Spinal Intact

- Infusion Start
- Bladder Pressure
- Voided Volume
- Infusion Stop

- Bladder Pressure: 25 cmH₂O
- Voided Volume: 25 ml
- Infusion Start: 10 min
- Voiding efficiency: 95.2%
- Infusion rate: 0.5 ml/min
- Total infused: 21 ml

B. Chronic SCI

- Infusion Start
- Bladder Pressure
- Voided Volume
- Infusion Stop

- Bladder Pressure: 25 cmH₂O
- Voided Volume: 25 ml
- Infusion Start: 5 min
- Voiding efficiency: 5.4%
- Infusion rate: 4 ml/min
- Total infused: 74 ml
Voiding Induce by Continuous Infusion in SCI Cats

A. Continuous infusion

- Infusion Start
- Bladder Pressure
- Voided Volume
- 20 ml in bladder
- 19 ml in bladder
- Total infused: 57 ml
- Total voided: 38 ml

B. Larger bladder volume

- Infusion Start
- Infusion Stop
- Bladder Pressure
- Voided Volume
- 3 Hz, 8 V, 0.2 ms
- Total infused: 124 ml
- Total voided: 31 ml

Voiding efficiency: 25%
Voiding Induce by Stimulating and Blocking Pudendal Nerves

A. Bilateral Block during Continuous 20 Hz

- Bladder Pressure
- Voided Volume
- Infusion Start
- Infusion Stop (10 kHz, 10 mA)
- 20 Hz, 2 V, 0.2 ms
- 80 sec
- Total infused: 24 ml
- Total voided: 12 ml
- Voiding efficiency: 50%

B. Continuous 20 Hz during Bilateral Block

- Bladder Pressure
- Voided Volume
- Infusion Start
- Infusion Stop (10 kHz, 10 mA)
- 20 Hz, 2 V, 0.2 ms
- 80 sec
- Total infused: 25 ml
- Total voided: 22 ml
- Voiding efficiency: 88%
Voiding Efficiency

- Spinal intact
- Control
- 20Hz+block2

SCI

* Indicates significant difference.
Summary

• Voiding efficiency induced by bladder distension is very low in SCI cats compared to the normal cats.

• 20 Hz pudendal nerve stimulation by itself failed to induce voiding.

• Efficient voiding can be induced in SCI cats by 20 Hz pudnedal nerve stimulation combined with 10 kHz nerve block bilaterally.
Design and Development of a Small Implantable Pudendal Nerve Stimulator

US patent application # US/2009/0036945
Methods and Systems for Achieving a Physiological Response by Pudendal Nerve Stimulation and Blockade
Filing Date: August 1, 2008. Publication Date: February 5, 2009.
An Implantable Bladder “Pacemaker”

Figure 1: Our strategy to restore normal functions of the lower urinary tract after SCI. EUS – External Urethral Sphincter.

Figure 1: Our strategy to restore normal functions of the lower urinary tract after SCI. EUS – External Urethral Sphincter.
An Implantable Bladder “Pacemaker”

External Control Device
- Display
- Keyboard
- Transceiver
- Control Unit

External Charging Device
- Wireless
- Underneath Skin

Implanted Stimulator
- Transceiver
- Control Unit
- Rechargeable Power Supply
- Power Amplifier
- Output Channels #1, #2, #3

External Handhold Device
- Setting the storage/voiding mode
- Setting each channel individually
- Wearable

Implanted Stimulator
- Channel #1: 1-10 Hz or 20-40 Hz
- Channel #2/3: 6-10 kHz
- Small Size: < 5x5x1 cm
- Power Supply: > 5 years, wireless charging
- Communication: wireless

Figure 11: Diagram of the control device and the implantable stimulator.
An Implantable Bladder “Pacemaker”

Wireless controlled, battery powered
But not wireless charged

Version #1

Version #2

Antenna

Battery
An Implantable Bladder “Pacemaker”

![Diagram of implantable stimulator](image)

- Cuff Electrode #1
- Cuff Electrode #2/#3
- Stimulator
- Battery
- USB Controller

Wireless controlled, wireless charged, battery powered, implantable stimulator
Bladder “Pacemaker” – Improving Storage

Start infusion

Stop infusion

5 Hz, 4 V, 0.2 ms

Stop stimulation

2 min

90 cmH₂O
Bladder “Pacemaker” – EUS Blockade

Start Infusion

Bladder pressure

Stop Infusion

Voided volume

10 kHz, 6 V

20 Hz, 0.6 V, 0.2 ms

1 min

40 cm H₂O

10 mL
Bladder “Pacemaker” – Low Pressure Voiding

Infused: 8.5 mL, Voided: 7.5 mL, Efficiency: 88%
An Implantable Bladder “Pacemaker” in Human

- Develop the bladder “pacemaker” for FDA IDE approval
- Clinical trial in human SCI subjects
- Additional funding
Acknowledgement

Department of Urology
University of Pittsburgh
Marc Rogers, M.D.
Jeremy Reese, M.D.
Jeffery Larson, M.D.
P. Dafe Ogagan, M.D.
Abhijith Dev Mally, M.D.
Bing Shen, D.V.M.
Jicheng Wang, Ph.D.
Hailong Liu, Ph.D.
Fan Zhang, M.D.
Guoqing Chen, M.D.
Shouguo Zhao, Ph.D.
Shaohua Huang, Ph.D.
Yosuke Matsuta, M.D., Ph.D.
Zeyad Schwen, B.S.
Guangning Yang, B.S.
Zhiying Xiao, M.D.

Department of Pharmacology & Chemical Biology
University of Pittsburgh
Xianchun Wang, M.D.
Timothy Ungerer, B.S.
James R. Roppolo, Ph.D.
William C. de Groat, Ph.D.

Department of Defense (DOD)
Christopher and Dana Reeve Foundation

National Institute of Diabetes & Digestive & Kidney Diseases (NIDDK)